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09/873,546	06/04/2001	Geoff J. Clark	NIH-05080	7592
23535	7590	05/19/2004	EXAMINER	
MEDLEN & CARROLL, LLP 101 HOWARD STREET SUITE 350 SAN FRANCISCO, CA 94105			SCHNIZER, RICHARD A	
			ART UNIT	PAPER NUMBER
			1635	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/873,546

Applicant(s)

CLARK ET AL.

Examiner

Richard Schnizer, Ph. D

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 26 April 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-4,6-16 and 29-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-4,6-16 and 29-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on 31 July 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/26/04 has been entered.

Claims 30-39 were added as requested.

Claims 1-4, 6-16, 29-39 are pending in the application and under consideration in this Office Action.

### ***Rejections Withdrawn***

The rejection of claims 1 and 4 under 35 USC 102(b) over Lamerdin et al is withdrawn in view of Applicant's amendments.

The rejection of claims 6-15 and 29 under 35 U.S.C. 102(b) as being anticipated by Yu et al (Proc. Nat. Acad. Sci. USA 96: 214-219, 1999) is withdrawn in view of Applicant's amendments.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 34-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32, 34, 37, and 39 are indefinite because they are drawn to compositions, but only recite a single component. For example claim 32 recites only "the purified nucleic acid of claim 30." A composition must comprise more than one component, as such, the claims are incomplete.

Claims 35-39 are indefinite because it is unclear what is intended by "substantially homologous." The specification fails to give this term a limiting definition such that one of skill in the art could understand the metes and bounds of the claim. For example the specification teaches that the term can be used to refer to any sequence that is partially complementary to another sequence, but fails to identify any lower limit on the degree of identity necessary to qualify as "substantially homologous". See e.g. paragraphs 50, 53, and 54.

Claims 35-39 are indefinite because they recite "the derivative" without antecedent basis. It is also unclear what is intended by "the derivative comprises an amino acid substitution in SEQ ID NO:5". As the Examiner understands the claim, the "derivative" is not SEQ ID NO:5, so it cannot possess a substitution in SEQ ID NO:5.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***New Matter***

Claims 1-4 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4 as amended introduce new matter into the disclosure. These claims are drawn to recombinant expression vectors consisting of an open reading frame encoding SEQ ID NO:5 operably linked to one or more regulatory elements. The specification as filed does not provide written support for any vector consisting only of regulatory sequences operably linked to a nucleic acid encoding SEQ ID NO:5.

It is conventional within the art to use viral vectors (e.g. gutted viral vectors) that comprise regulatory sequences that affect the expression or replication of heterologous genes of interest, but no viral genes. For example, the specification discloses the use of adeno-associated virus vectors which typically are used without any viral genes. However even these vectors comprise sequences, such as terminal inverted repeats and packaging signals, which are not regulatory in nature and would place these vectors outside the scope of the instant claims. Further, claims 1, 2, and 4 are not limited to viral vectors, and the specification contemplates plasmid vectors and other non-viral vectors broadly such that these claims could fairly be interpreted as being drawn to plasmid or cosmid vectors consisting only of regulatory sequences in operably linkage with a nucleic acid encoding SEQ ID NO:5. But, the specification fails to teach

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any such vector, e.g. the specification fails to teach a plasmid expression vector lacking a selectable marker, although it is conventional in the art for such elements to be included in plasmid expression vectors. For these reasons, claims 1-4 are considered to comprise new matter

Claims 35-39 are drawn to a nucleic acid molecule that is substantially homologous to a nucleic acid molecule encoding SEQ ID NO:5, wherein the claimed nucleic acid molecule encodes a derivative of SEQ ID NO:5 comprising an amino acid substitution relative to SEQ ID NO:5. The claims require that the encoded polypeptide must have tumor growth inhibiting activity, focus formation inhibiting activity, and an ability to bind to Raf-1. The claims do not limit the amount of amino acid substitutions that may be made in SEQ ID NO:5, nor the nature of tumors or foci that may be inhibited. As such the claims embrace the genus of nucleic acids encoding polypeptides that are at least as long as SEQ ID NO:5 and that have the recited functional characteristics.

At page 7 of the submission filed 1/26/04, Applicant points for support in the specification to page 11, lines 1-7, page 15, line 24, through page 16, line 8, page 21, line 19, through page 22, line 25, page 4, line 29, page 32, lines 16-23, page 12, line 25, through page 13, line 5, and Examples 5, 7, 8, and 10. However, none of these passages, nor the specification as filed, provides written support for a nucleic acid molecule that is substantially homologous to a nucleic acid molecule encoding SEQ ID NO:5, wherein the claimed nucleic acid molecule encodes a derivative of SEQ ID NO:5

comprising an amino acid substitution relative to SEQ ID NO:5. As such these claims constitute new matter.

### ***Written Description***

Claims 35-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 35-39 are drawn to the genus of nucleic acids encoding polypeptides that vary from SEQ ID NO:5 by at least one amino acid substitution, and which bind Raf-1, inhibit focus formation, and inhibit tumor growth. Thus the claims do not limit the structure of the polypeptide in any way, except that it must be of at least equal length to SEQ ID NO:5.

The written description requirement can be satisfied for genus claims by disclosure of a representative number of species of the claimed genus. Disclosure may be by reduction to practice, drawings, or complete structural description, or by disclosure of relevant identifying characteristics such as a known or disclosed correlation between structure and function that is common to the members of the genus. The instant specification discloses an S21N mutation of SEQ ID NO:5 (analogous to Ras S17N) causes transformation when expressed in NIH 3T3 cells, but fails to disclose a single variant of SEQ ID NO:5 that comprises the functions recited in claims 35-39.

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Further, the specification fails to disclose any relevant identifying characteristic such as any correlation between any polypeptide structure and any of the required functions. As such one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time of filing.

### ***Enablement***

Claims 35-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated or purified nucleic acids encoding SEQ ID NO:5, does not reasonably provide enablement for nucleic acids encoding polypeptides other than SEQ ID NO:5 that function to inhibit focus formation, inhibit tumor growth, and bind to Raf-1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 35-39 are drawn to the genus of nucleic acids encoding polypeptides that vary from SEQ ID NO:5 by at least one amino acid substitution, and which bind Raf-1, inhibit focus formation, and inhibit tumor growth. Thus the claims do not limit the structure of the polypeptide in any way, except that it must be of at least equal length to SEQ ID NO:5.

The specification provides guidance as to the function of SEQ ID NO:5. This protein is expressed in fetal and adult brain and heart, but not in a variety of other tissues. Expression is reduced or zero in some tumor derived neuronal cell lines and tumor-derived tissue samples, but appears normal in others (see e.g. Fig. 12, lanes 3,

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4, 6, and 9-12). Constitutive expression of SEQ ID NO:4 inhibits focus formation in NIH 3T3 cells. The protein antagonizes Ras-dependent Elk-1 transcription factor activity, and inhibits the growth of U251 and A673 neuronal tumor-derived cells when expressed ectopically in these lines. An S21N mutation of SEQ ID NO:5 (analogous to Ras S17N) causes transformation when expressed in NIH 3T3 cells. Finally, SEQ ID NO:5 coprecipitates with Raf-1, a kinase which is regulated by H-Ras and K-Ras. However, the specification fails to teach what are the minimum sequence and functional characteristics a given polypeptide must have in order to perform these functions. For example, the specification teaches that Noey2 is a related polypeptide (63% identity, see page 44, lines 24-29) that is similar to SEQ ID NO:5 inasmuch as it is a G-protein and appears to be a tumor suppressor. A search of the prior art provided no evidence that Noey2 bound Raf-1, and the specification fails to teach what structures in SEQ ID NO:5 are responsible for Raf-1 binding.

At the time the invention was filed the Ras protein superfamily contained about 150 members which functioned to transduce a wide variety of signals in cells. See Paduch et al (*Acta Biochemica Polonica* 48(4): 829-850, 2001) page 830, column 1, first line of last paragraph. These proteins all comprise a guanine nucleotide binding domain with a high affinity for GTP or GDP, and low (but extremely variable within the superfamily) catalytic activity. The nucleotide binding site also contributes to the binding of effector molecules which are activated by Ras and which mediate the wide variety of cellular responses. The phosphorylation state of the nucleotide in the binding site regulates the activity of the Ras protein, (GDP activates Ras, and GTP inactivates Ras),

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and influences recognition and binding of effector molecules. So, structural differences between Ras molecules govern the rate at which GTP is hydrolyzed as well as the identity of effector molecules with which they interact, and consequently the nature of signals that are transduced. See page 833, column 1, last full paragraph of Paduck. Although various Ras nucleotide binding sites are well known and highly conserved, it is unclear what governs the substantial kinetic differences in GTP/GDP exchange observed in the various Ras proteins. While the Raf-1 binding site of Rap-1A is known in the art (see Paduch at paragraph bridging pages 837 and 838), the specification does not disclose the Raf-1 binding site of SEQ ID NO:5, or what amino acids can be mutated substituted while preserving this function, as well as the other claimed functions.

Generally speaking, the effects of amino acid substitutions on polypeptide activity are unpredictable. While it is known that many amino acid substitutions are generally possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. These or other regions may also be critical determinants of activity. These regions can tolerate only relatively conservative substitutions, or no substitutions. See Bowie et al (1990). The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide

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Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". In the specific case of Ras proteins, Paduck teaches that the effects on the activity of the protein of mutations in the nucleotide binding site are unpredictable. Furthermore, site directed mutagenesis studies have shown that mutations affecting nucleotide binding, and therefore signal transduction, are not limited only to the nucleotide binding site, but are found in segments well outside the nucleotide binding site. See paragraph bridging columns 1 and 2 on page 834. Because neither the prior art nor the specification provides adequate guidance as to how to generally predict the effects of amino acid substitutions within even the highly conserved nucleotide binding site of Ras proteins, and because the specification fails to teach what are the structural limitations that define Rig polypeptides, one of skill in the art could not determine without undue experimentation what sequences other than SEQ ID NO:5 comprise the claimed activities of SEQ ID NO:5, and could not make such proteins without undue experimentation. One might argue that it would not be undue experimentation to express and assay polypeptides individually using the assays taught in the specification,

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and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will adequately maintain SEQ ID NO:5 structure and function. In the absence of such guidance, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 6-11, 13-15, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) in view of Kimmelman et al (Oncogene (1997) 15(22): 2675-2685).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including an open reading frame encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins.

Lamerdin does not teach a method of detecting in a sample nucleic acids by Northern blot using a probe having complementarity to a portion of the nucleotide sequence of SEQ ID NO:4, a method of amplifying nucleic acids by using PCR primers for amplifying SEQ ID NO:4, or a nucleic acid consisting of an open reading frame encoding SEQ ID NO:5.

Kimmelman teaches the cloning of a Ras-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and methods of detecting the corresponding mRNA in a variety of human tissues by Northern blot of total cellular RNA. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681. It is noted that total cellular RNA comprises polyA RNA.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the Northern blot method of Kimmelman to detect nucleic acids encoding SEQ ID NO:5 in human tissues, including tumor tissues, using a probe comprising at least a portion of SEQ ID NO:4. One would have been motivated to do so because it is apparent from the teachings of Kimmelman that determining the pattern of expression of newly discovered Ras-related genes is essential to understanding their function, and because Kimmelman teaches that Ras-related genes are involved in tumorigenesis and are therefore of biomedical interest. See abstract, page 2676, column 1, last paragraph prior to Results, and paragraph bridging pages 2680 and 2681.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PCR amplification to transfer the open reading frame of Lamerdin from the bacterial artificial chromosome to an expression vector as taught by Kimmelman. See page 2682, column 2, lines 1-10 of paragraph bridging pages 2682 and 2683. One would have been motivated to do so because PCR allows one to insert restriction enzymes of choice onto the termini of a given open reading frame, as evidenced by Kimmelman who used PCR primers containing BamHI or EcoRI sites, thereby facilitating insertion into a vector of choice in an orientation of choice.

Thus the invention as a whole was *prima facie* obvious.

Claim 12 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 6-11, 13-15, and 29 above, and further in view of Mullis et al (US Patent 4,965,188, issued 10/23/90), and Takarada (US patent 5,981,183, issued 11/9/99).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

These references do not explicitly teach a DNA polymerase comprising both DNA- dependent DNA polymerase activity and RNA-dependent DNA polymerase activity.

Mullis teaches amplification of DNA sequences by polymerase chain reaction (PCR), using DNA polymerase from *Thermus aquaticus*. See e.g. claim 5.

Takarada teaches that DNA polymerase from *Thermus aquaticus* comprises both DNA dependent DNA polymerase activity and RNA dependent DNA polymerase activity. See column 9, lines 62-67.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the *Thermus aquaticus* DNA polymerase of Mullis to amplify the sequence of Lamerdin as taught by Kimmelman. One would have been motivated to do so because *Thermus aquaticus* DNA polymerase is stable at the high temperatures required for denaturation in PCR. See abstract of Mullis. The limitations of claim 12 are met because *Thermus aquaticus* DNA polymerase inherently comprises both DNA dependent DNA polymerase activity and RNA dependent DNA polymerase activity. See Takarada.

Thus the invention as a whole was *prima facie* obvious.

Claim 15 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 6-11, 13-15, and 29 above, and further in view of Mullis et al (US Patent 4,965,188, issued 10/23/90).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of

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SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

These references do not explicitly teach a method of amplifying RNA, as recited in claim 15.

Mullis teaches that PCR amplification of messenger RNA sequences allows an improvement in detection of target sequences without the use of radioactive labels. See column 7, lines 16-24 and paragraph bridging columns 19 and 20.

It would have been obvious to one of ordinary skill in the art at the time of the invention amplify mRNA sequences by PCR in order to characterize the pattern of tissues in which the sequence of Lamerdin was expressed, rather than Northern blotting as taught by Kimmelman. One would have been motivated to do so because PCR allows greater sensitivity and would have obviated the need for the radioactive label use by Kimmelman.

Thus the invention as a whole was *prima facie* obvious.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 1, 6-11 13-15, and 29 above, and further in view of Erlich et al (US Patent 5,314,809, issued 5/24/94) and DeBoer et al (US Patent 5,397,703, issued 3/14/95).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

Erlich teaches that PCR primers may be modified by the inclusion of G and or C residues at their 5' ends in order to improve thermostability. See column 3, lines 35-42.

DeBoer teaches the modification of PCR primers to include both a 5' C-G clamp and a restriction site. See column 14, lines 9-11.

These references do not teach a oligonucleotides comprising SEQ ID NOS:2 and 3.

It would have been obvious to one of ordinary skill in the art at the time of the invention to synthesize for PCR oligonucleotide primers comprising SEQ ID NOS:2 and 3. One would have been motivated to do so in order to transfer the sequence of Lamerdin from a bacterial artificial chromosome to a plasmid expression vector having a higher transfection efficiency. In order to amplify and transfer the sequence of Lamerdin, one would have chosen primers corresponding to the 5' and 3' ends of the ORF of Lamerdin, as in SEQ ID NOS: 2 and 3. Additionally one would have been motivated to include restriction sites 5' to the portions of the primers corresponding to the ORF, in order to facilitate cloning of the resulting PCR fragment. For example, Kimmelman teaches the incorporation of Bam HI and Eco RI sites, as are incorporated into instant SEQ ID NOS: 2 and 3, respectively. See lines 1-10 of paragraph bridging

pages 2682 and 2683 of Kimmelman. Finally, it is routine in the art to add G and or C residues to the 5' ends of primers in order to increase the thermostability of the primers. This is apparent from the teachings of both Erlich and DeBoer. In fact DeBoer teaches the combination of restriction sites and G/C clamps at the 5' prime ends of PCR primers.

Thus the invention as a whole was *prima facie* obvious.

Claims 30-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) and Kimmelman et al (Oncogene (1997) 15(22): 2675-2685) as applied to claims 6-11, 13-15, and 29 above, and further in view of the 1997/1998 Stratagene catalog.

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Kimmelman teaches the cloning of a RAS-related gene by PCR amplification, transfer of the gene to a plasmid expression vector, analysis of expression of the encoded protein in eukaryotic cells, and detection of the corresponding mRNA in a variety of human tissues. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

These references do not teach a nucleic acid molecule consisting of an open reading frame encoding SEQ ID NO:5.

It would have been obvious to one of ordinary skill in the art at the time of the invention to isolate an open reading frame **comprising** SEQ ID NO:5 in the process of subcloning the open reading frame of Lamerdin et al. One would have been motivated to subclone the open reading frame of Lamerdin because Lamerdin noted that the open reading frame encoded a Ras-related protein, and because Kimmelman taught that

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Ras-related genes are involved in tumorigenesis and are therefore of biomedical interest, and determining the pattern of expression of newly discovered Ras-related genes is essential to understanding their function. See abstract, page 2676, column 1, last paragraph prior to Results, and paragraph bridging pages 2680 and 2681. In subcloning the open reading frame of Lamerdin, one of ordinary skill in the art would have been motivated to use a kit such as the pCR-Script™ cloning kit from Stratagene (see pages 98 and 99 the 1997/1998 Stratagene catalog) because this kit gives rise to blunt-ended PCR fragments that allow cloning into any expression vector comprising a restriction site positioned downstream of a promoter. One of ordinary skill in the art appreciates that the restriction sites that are not naturally cleaved to yield blunt ends, can be made blunt ended by treatment with "polishing" enzymes such as are provided in the pCR Script kit. Finally, one of skill in the art would have been motivated to use PCR primers that gave rise to a product **consisting of** the open reading frame of Lamerdin because, with the PCR-Script kit, there is no need reason to add additional 5' or 3' sequences.

Claim 31 is included in this rejection because although the open reading frame of Lamerdin differs from SEQ ID NO:4 by a single base at position 420, this difference is silent, resulting in a CAG rather than a CAA codon. However, CAA and CAG codons are recognized in the art as equivalent because they both encode glutamine. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Hence it would have been prima facie obvious to

one of ordinary skill in the art to substitute a CAA codon for the CAG codon of Lamerdin, resulting in a nucleic acid consisting of SEQ ID NO:4.

### ***Response to Arguments***

Applicant's arguments filed 4/26/04 have been fully considered but they are not persuasive.

Applicant argues that claims 6 and 11 and dependents require detecting an amplifying a nucleic acid encoding SEQ ID NO:5, and that none of the cited art teaches these steps. This is unpersuasive because Applicant has not addressed the Examiner's stated motivation for combining the references. As stated above in the rejection, Kimmelman provides motivation to subclone and express Ras-related open reading frames because Ras-related genes are involved in tumorigenesis and are therefore of biomedical interest, and determining the pattern of expression of newly discovered Ras-related genes is essential to understanding their function. For this reason the rejections are maintained.

### ***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

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If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 571-272-0564.



DAVE T. NGUYEN  
PRIMARY EXAMINER

Richard Schnizer, Ph.D.

(FILE 'HOME' ENTERED AT 13:59:28 ON 11 MAY 2004)

FILE 'MEDLINE' ENTERED AT 13:59:35 ON 11 MAY 2004

- L1 1 SEA PLU=ON (RAF-1 (3A) BIND?) AND FOCUS AND INHIBIT?  
D BIB AB
- L2 111 SEA PLU=ON (MEK OR ERK) AND FOCUS  
D BIB AB 100-111
- L3 0 SEA PLU=ON NOEY
- L4 6 SEA PLU=ON NOEY2
- L5 0 SEA PLU=ON L4 AND RAF?
- L6 128 SEA PLU=ON RAF-1 (3A) (BIND? OR BOUND)
- L7 0 SEA PLU=ON L6 AND (FOCUS (3A) FORM)
- L8 0 SEA PLU=ON L6 AND (FOCUS (3A) FORM?)
- L9 1 SEA PLU=ON L6 AND (FOCUS OR FOCI)  
D BIB AB

FILE 'CAPLUS, EMBASE, BIOSIS, BIOTECHDS, SCISEARCH' ENTERED AT  
14:09:25  
ON 11 MAY 2004

- L10 8 SEA PLU=ON L5 OR L7 OR L8 OR L9
- L11 5 DUP REM L10 (3 DUPLICATES REMOVED)  
D BIB AB 1-5
- L12 3039 SEA PLU=ON (MEK OR ERK) AND DOMINANT NEGATIVE
- L13 351 SEA PLU=ON L12 AND RAF-1
- L14 18 SEA PLU=ON L13 AND (BIND? OR BOUND)(5A) RAF-1  
D TI 1-18
- L15 6 DUP REM L14 (12 DUPLICATES REMOVED)  
D BIB AB 1-6

(FILE 'HOME' ENTERED AT 14:44:47 ON 11 MAY 2004)

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,  
BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHDS, BIOTECHNO, CABA,  
CANCERLIT,  
CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DISSABS,  
DGENE,  
DRUGB, DRUGMONOG2, IMSDRUGNEWS, DRUGU, IMSRESEARCH, ..'  
ENTERED AT  
14:44:58 ON 11 MAY 2004

- L1 113 SEA PLU=ON NOEY2
- L2 5 SEA PLU=ON L1 AND RAF-1

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L3        3 DUP REM L2 (2 DUPLICATES REMOVED)  
           D KWIC 1-3  
           D BIB AB 1-3

S #	Updt	Database	Query	Time	Commen
<u>S12397</u>	<u>U</u>	USPT	5523221.pn.	2004-05-11 13:22:06	
<u>S12396</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	pcr same blunt same pfu same ligat\$	2004-05-11 13:02:59	
<u>S12395</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	pcr and blunt same pfu	2004-05-11 12:59:45	
<u>S12394</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	pcr same blunt same pfu same orient\$	2004-05-11 12:57:19	
<u>S12393</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	orinetation same pcr same blunt same pfu	2004-05-11 12:57:06	
<u>S12392</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	pcr same blunt same pfu	2004-05-11 12:56:52	
<u>S12391</u>	<u>U</u>	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	pcr same blunt same exonuclease same orientation	2004-05-11 12:51:30	
<u>S12390</u>	<u>U</u>	PGPB	pcr same blunt same exonuclease same orientation	2004-05-11 12:51:20	
<u>S12389</u>	<u>U</u>	PGPB	20030059771 and stringen\$	2004-05-11 11:52:10	
<u>S12388</u>	<u>U</u>	PGPB	20030059771 and (identi\$ or similar\$ or	2004-05-11 10:54:21	

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S12387   U   PGPB

homolog\$)  
20030059771 2004-  
and (identi\$ 05-11  
or similar\$ or 10:54:09  
hmolog\$)

S12386   U   PGPB

20030059771 2004-  
and (focus or 05-11  
tumor) 10:51:19

S12385   U   PGPB

20030059771 2004-  
and 05-11  
substitut\$ 10:29:50

S12384   U   PGPB

20030059771 2004-  
and 05-11  
substantial\$ 10:14:43

S12383   U   PGPB

20030059771 2004-  
and 05-11  
regulatory 10:00:26